IMMUNE DEFICIENCIES, ALLERGY

ALLERGY

DEFINITIONS

**Allergy** is a pathologically altered, enhanced immunological reactivity to antigens (allergens).

**Atopy** is a propensity to develop one or more IgE mediated diseases (bronchial asthma, allergic, rhinitis, eczema), often in familiar clustering. Atopy can be inherited (with the 11th chromosome).

Immune reactions involved in allergic diseases

**Type I immunoreaction**

1. **Initial sensitization**: first encounter of antigen → formation of specific IgE
   
   IL-4 → production of IgE

   Binding of IgE to high affinity FcεR of mast cells and basophils

2. **Allergic phase**: second and further encounters with the antigen → combination of antigen with IgE
   
   → degranulation of basophils and mast cells

   → release of mediators by IgE or other mechanisms (early, late phases)

**Type III, IV immunoreactions**

THE MOST IMPORTANT MEDIATORS RELEASED DURING DEGRANULATION OF MASTOCYTES

**Chemotactic mediators**: Neutrophil chemotactic factor (NCF), eosinophil chemotactic factor A (ECF-A), leukotriene B4 (LTB4)

**Proteolytic enzymes**: Histamine, tryptase, kininogenase

**Spasmogenic mediators**: Histamine, prostaglandin D2 (PGD2) leukotriene C4 (LTC4), leukotriene D4 (LTD4), platelet activating factor (PAF)

**Other mediators**: Heparin

LIST OF ALLERGIC DISEASES

**Systemic**: Anaphylaxis, serum sickness

**Skin and mucous membranes**: Atopic dermatitis, urticaria, angioedema, eczema, contact dermatitis, allergic vasculitis

**Upper respiratory tract**: Allergic rhinitis, nasal polyps, sinusitis

**Lung**: Bronchial asthma, hypersensitivity pneumonitis (extrinsic allergic alveolitis), allergic bronchopulmonary aspergillosis

**GI tract**: Food allergy

Drug allergy can be systemic or can involve several organs: skin, lung, liver, kidney, bone marrow and blood cells

THE DIAGNOSIS OF ALLERGIC DISEASES

1. **History and physical examination**

2. **In vivo diagnostic procedures**

   **Skin tests**

   - Immediate type: Prick test
   - Immediate type with late phase reaction: Arthus reaction
   - Late phase: epicutaneous, intracutaneous

   **Other provocation tests**:

   - Nasal, conjunctival provocation
• Bronchial provocation tests: Aspecific (histamine, acetylcholine, KCl, adenosine), exercise-induced, Allergen-specific (occupational materials)
• Broncholytic tests (with β-mimetics)
• Food challenge: DBPCFC: double blind placebo-controlled food challenge

3. In vitro diagnostic procedures
• Determination of IgE and IgG4 concentrations:
  • Total and specific IgE, IgG4 - radio-allergosorbent test (RAST)

Determination of immune activation in presence of allergen:
  • Lymphoblastic transformation (LBT)
  • Chromatin activation method

Determination of mediators in body fluids
  • Eosinophils, ECP, PAF in bronchoalveolar lavage (BAL), nasal and conjunctival fluids
  • Fecal IgE, allergen-specific IgE, IgG, ECP

ANAPHYLAXIS

Definitions
Anaphylaxis is a life-threatening response of a sensitized individual, which appears within minutes after administration of specific antigen which manifests by respiratory distress, vascular collapse or shock.

Anaphylactoid reaction: systemic reaction with the same symptoms as anaphylaxis, but are not due to an IgE-dependent mechanism and are usually not immune.

Pathomechanism
Type I immunoreaction

Agents causing anaphylaxis
Proteins
• Heterologous proteins in the form of antiserum (mainly horse and rabbit serum): tetanus, diphtheria antitoxin, anti-lymphocyte globulin
• Venoms: Hymenoptera
• Pollens (ragweed, grass, etc.), pollen extracts
• Foods (eggs, seafood, nuts, grains, beans, cottonseed oil, chocolate)
• Human proteins: serum proteins, seminal fluid
• Hormones: insulin, ACTH, vasopressin, parathormone
• Enzymes: trypsin, penicillinase

Haptens and other low MWT substances
• Antibiotics: penicillins, sulfonamides, cephalosporins, tetracyclines, amphotericin B, nitrofurantoin, aminoglycosides
• Local anesthetics: lidocaine, procaine, etc.

Polysaccharides: Dextran, iron dextran.

Other drugs causing anaphylactoid reaction: NSAID-s, radiographic contrast materials.
• Insect sting allergy: Type I immunoreaction to venoms of insects (phospholipase A) in the Hymenoptera order: bees: honeybees, bumblebees, Vespids: yellow jackets, hornets, wasps

Clinical manifestations
Onset within seconds to minutes after induction of the antigen!
• Circulatory system: skin erythema, feeling of warmth and/or impending doom, light-headedness, myocardial ischemia, ventricular arrhythmias, vascular collapse, shock.
• Upper and/or lower airway obstruction: Laryngeal edema: "lump" in the throat, hoarseness, stridor; Lung: tightness in the chest, shortness of breath, wheezing, pO2 ↓, pCO2 ↑.
• Cutaneous: urticaria, angioedema. May coalesce to giant hives. Swelling of face, eyes, lips, tongue, pharynx or extremities.
• Gastrointestinal: nausea, vomiting, abdominal cramps, diarrhea.
• Central nervous: delirium, seizures.

The diagnosis of anaphylaxis

Diagnosis: accurate history: timing, RAST.

Differential diagnosis:
Acute myocardial infarction, pulmonary embolism, acute asthma, hereditary angioedema, cold urticaria, seizure disorder, toxicologic response, vasovagal reaction.

Anaphylactoid or idiosyncratic response
E.g., chemical mast-cell degranulating agent (opiates, tubocurare, dextrans, sulfobromophthalein), NSAID-s in asthma (PG/LT imbalance when COX is inhibited).
Transfusion reaction (especially in IgA deficiency: IgG type anti-IgA antibody → complement activation → secondary mast cell degranulation)

Treatment of anaphylaxis

EARLY RECOGNITION IS MANDATORY!
• Mild symptoms - pruritus, urticaria: 0.2-0.5 mL (0.01 ml/kg) of 1:1000 epinephrine IM, if needed, repeat at 3-20 min intervals for severe reaction.
• If an extremity was injected - prompt application of a torquinet proximal to the reaction site, administration of 0.2 mL of 1:1000 epinephrine into the site; remove the insect sting without compression!
• If hypotension occurs - 5 mL of epinephrine 1:10,000 IV
  o OR: infusion of epinephrine 1:50,000
  o volume expanders, vasopressor agents (e.g. dopamine 2-20 mg/kg/min)
• If epinephrine fails - consider hypoxia due to airway obstruction or cardiac arrhythmia
  o oxygen via a nasal catheter
  o intermittent positive pressure breathing of oxygen with 0.5 mL isoproterenol in 1:200 saline
  o endotracheal intubation or tracheostomy is mandatory, if hypoxia is progressive!
  o intravenous line, Swan-Ganz catheter
  o The Epinephrine Auto-Injector (EpiPen)
• Ancillary agents:
  o antihistamines, eg. diphenhydramine 50-80 mg IM or IV (for urticaria-angioedema)
  o methylxantines, eg. aminophylline 0.25-0.5 g (6 mg/kg loading dose, followed by 0.5-1 mg/kg/h) IV, inhaled b2 sympathomimetics (for bronchospasm)
  o corticosteroids (eg. prednisolone 100 mg IV) - not effective for the acute event.

Prevention of anaphylaxis
• Avoidance of allergen (eg. food, drug, pollen)
• Medic-Alert bracelet
• Select an other agent or procedure
• Skin test - before the administration of highly allergenic materials: (eg. horse serum, allergic extracts)
• Since even a skin or conjunctival test can produce a serious reaction, a scratch test should be done first!
• Hyposensitization is mandatory in case of the Hymenoptera venom.
URTICARIA AND ANGIOEDEMA

Definitions

**Urticaria** is an itching, elevated, erythematous, well-circumscribed, pruritic wheals (hives), or serpiginous exanthem, usually surrounded by erythema. Its center blanches on pressure. It appears on any epidermal and mucosal surfaces, usually on the trunk, extremities, sparing the palms and soles. Caused by subcutaneous or intradermal leakage of fluid.

**Angioedema** is a brawny nonpitting edema, usually without well-defined margins, involving the epidermal and mucosal surfaces: lips, tongue, eyelids, genitals, dorsum of the hands. Caused by leakage of fluid in deeper (dermal, subdermal) layers.

Both are self-limited, evanescent in nature. Urticaria + angio-edema: 50%, urticaria alone: 40%, angioedema alone: 10%

**Acute urticaria, angioedema:** lasting < 6 weeks
**Chronic urticaria, angioedema:** > 6 weeks

Pathogenesis and pathology

Type I immunoreaction: IgE → mast cell degranulation
C3a, C4a, C5a, C2b → PG, HETE, LTC, LTD, LTE, PAF
bradykinin, SP

**Histology:** subcutaneous edema, flattened rete pegs, widened dermal papillae, swollen collagen fibres, increased number of cutaneous mast cells.
In chronic urticaria: ↑ CD4, ↑ Eo, few Mo/Mφ
in a minority: leukocytoclastic vasculitis

Classification

1 IgE-dependent
   a) Atopic diathesis
   b) Specific antigen sensitivity (pollens, foods, drugs, fungi, moulds, Hymenoptera venom, helminths)
   c) Physical: dermographism; cold; light; cholinergic; vibratory; exercise-related

2 Complement-mediated
   a) Hereditary angioedema: type 1; type 2
   b) Acquired angioedema: type 1; type 2
   c) Necrotizing vasculitis
   d) Serum sickness
   e) Reactions to blood products

3 Nonimmunologic
   a) Direct mast cell-releasing agents: opiates; antibiotics; curare, d-tubocurarine; radiocontrast media
   b) Agents which presumably alter arachidonic acid metabolism: aspirin and NSAID-s; azo dyes and benzoates

4 Idiopathic

Differential diagnosis

Contact sensitivity, atopic dermatitis, erythrogenic porphyria, photoallergic reactions

Therapy

- Antihistamines, nifedipine, ketotifen, steroids,
- For management of acute very severe urticaria: epinephrine 1:10000, 0.2-0.3 ml SC
- Anti-IgE monoclonal antibody (omalizumab)
HEREDITARY ANGIOEDEMA (HAE)

Defect of C1-INH gene on chromosome 11.

**Inheritance:** AD: affects 50% of offsprings, M/F=1:1

**Symptoms**
Can start at any age. Is mild in childhood, become more severe at the time of puberty. Angioedema on extremities and genitalia, severe abdominal pain, respiratory obstruction → asphyxiation. Attacks are sporadic: local trauma, pressure (50%), emotional stress (50%), erythema marginatum (33%). Progressively more severe symptoms over 1.5 days, then regression over a similar time period. High incidence of autoimmune diseases, endocrinopathies, granulomatous bowel disease, arthritides, SLE.

**Pathogenesis**
HAE type I (80%): ↓ C1-INH level
HAE type II (15%): C1-INH is present, but is non-functional
Loss of control of 1) complement activation, 2) kinin, 3) fibrinolytic, 4) intrinsic clotting pathways.

**Diagnosis**
Low levels of C1-INH, ↓ C4/C2 (both during and between attacks), C3 is normal; C1 can also be normal

**Treatment**

*In acute attacks:*
- Purified C1-INH (Berinert H).
- Epinephrine 1:1000 in nebulizer, 0.2-0.3 ml sc, repeated 3 times in q 20-30 mins.
- Endotracheal intubation, tracheostomy.

*For long-term therapy:*
- Fresh frozen plasma.
- Acetylated androgens: danasol (200-400/d), stanozol, methyltestosterone (10-30 mg/d)
- ε-aminocapric acid

ECZEMA (DERMATITIS)

**Definition**
Eczema is an inflammatory response of the skin to multiple exogenous and endogenous agents.

**Clinical forms**

*Known causes:*
- Contact dermatitis (irritant, allergic contact), photodermatitis (allergic, contact), drug-induced, infectious, infectious, dermatophytid, autosensitization, xerotic eczema.

*Unknown causes:*
- Atopic, stasis dermatitis, lichen simplex chronicum (neurodermatitis), nummular, seborrheic, dyshidrotic, nonspecific eczema.

**Allergic contact dermatitis:** Caused by chemical agents that elicit type IV DTH on skin. Contact precedes rash by 2 or more days; site and configuration of eczema reaction conforms to site of contact with exogenous substances (plants, medicaments, cosmetics, metals).

**Photoallergic dermatitis:** UV light exposure plus topical or systemic substances induce type IV DTH. Eczematous reaction in sun-exposed areas of skin with sharp "cut-off" borders.

**Atopic eczema:** Hereditary disposition in association with familial tendency for asthma and allergic rhinitis. Eczematous reaction often localized to face, neck, antecubital and popliteal areas.

**Diagnosis**
History, epicutaneous (patch) intracutaneous skin tests, IgE, RAST

**Therapy**
Avoidance of allergen, wet dressings, topical steroids, emollients, systemic antihistamines
**Allergic rhinitis and conjunctivitis**

**Definition**
Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucous membranes. Frequently associated with bronchial asthma and eczema. Incidence: 5-10%

**Etiology**
- **Seasonal**: tree, grass pollens, ragweed.
- **Perennial**: mites (Dermatophagoides pteronyssimus, D. farinae), animals (danders, saliva, urine), mould spores, furs

**Symptoms**
- **Rhinitis**: nasal stuffiness, paroxysms of sneezing, profuse mucous secretion, frequent itching of the nose, eyes, posterior pharynx, periorbital swelling.
- **Conjunctivitis**: excessive tearing, mucoid discharge, itching
- **Constitutional**: fatigue, malaise, anorexia, irritability.
- Allergic "shiners", allergic "saluting".

**Complications**
Nasal polyps, serous otitis (hearing loss), chronic sinusitis (nocturnal cough, fever, headache)

**Diagnosis**
History, nasal examination, skin test, RAST, FAST, ELISA.

**Differential diagnosis**
Infectious, eosinophilic non-allergic, drug-induced, vasomotor rhinitides.

**Treatment**
- Avoidance of offending allergens
- Symptomatic treatment: antihistamines (1st, 2nd generation drugs), nasal decongestants (α-agonists) - only for a few days!, cromolyn sodium, topical corticosteroids
- Immunotherapy (hyposensitization)

**Bronchial asthma**

**Definition**
Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment. Chronic airway inflammation causes airway hyperresponsiveness to a variety of triggers, leading to airflow obstruction and respiratory symptoms including dyspnea and wheezing.

**Prevalence**
The prevalence of asthma has increased markedly over the past 30 years. In developed countries, approximately 10% of adults and 15% of children have asthma. Considerable overlap with allergic rhinitis. Common airways: ARIA

**Types of asthma**
- **Extrinsic**: Atopy, childhood-onset, allergic rhinitis and/or eczema, elevated IgE
- **Intrinsic**: No atopy, adult-onset, allergen tests are negative, normal IgE
- **Occupational**: Adult-onset, chemicals (toluene diisocyanate, trimellitic anhydride, etc.)

**Triggers of asthma**
- Inhaled allergens
- Viral upper respiratory tract infections
- Drugs: β-adrenergic blocking agents, NSAIDs (salicylates)
- Physical exercise
- Other: air pollution, occupational exposures, and stress
Symptoms

- Wheezing, dyspnea, and cough. These symptoms often vary widely within a particular individual, and they can change spontaneously or with age, season of the year, and treatment. Symptoms may be worse at night
- Indicators of inadequate asthma control: Nocturnal awakenings, need for systemic steroid treatment, hospitalization, and intensive care treatment

Physical examination

Wheezing and rhonchi throughout the chest, more prominent in expiration. In severe cases respiratory distress: tachypnea, use of accessory respiratory muscles, and cyanosis. Evidence of allergic nasal, sinus, or skin disease should be assessed. When asthma is adequately controlled, the physical exam may be normal.

Pulmonary function tests

**Spirometry** often shows airflow obstruction, with a reduction in the FEV1 and FEV1/FVC ratio. However, spirometry may be normal, especially if asthma symptoms are adequately treated. Bronchodilator reversibility is demonstrated by an increase in FEV1 by ≥200 mL and ≥12% from baseline FEV1 15–20 min after a short-acting β agonist (often albuterol MDI two puffs or 180 μg). Many but not all asthmatics will demonstrate significant bronchodilator reversibility; optimal pharmacologic treatment may reduce bronchodilator reversibility.

The peak expiratory flow rate (PEF) can be used by the patient to track asthma control objectively at home. Increases in total lung capacity and residual volume may be observed. The diffusing capacity for carbon monoxide is usually normal.

**Other tests**

- CBC may demonstrate eosinophilia.
- Specific IgE measurements for inhaled allergens (RAST) or allergy skin testing may assist in determining allergic triggers.
- Total serum IgE is markedly elevated in allergic bronchopulmonary aspergillosis (ABPA).

Radiologic findings

Chest x-ray is usually normal. In acute exacerbations pneumothorax may be identified. In ABPA, eosinophilic pulmonary infiltrates may be observed. Chest CT scan is not typically performed in routine asthma but may show central bronchiectasis in ABPA.

The differential diagnosis of asthma

- Upper airway obstruction by tumor or laryngeal edema (stridor)
- Endobronchial tumor or foreign body (localized wheezing in the chest)
- Chronic heart failure (bibasilar crackles)
- Eosinophilic pneumonias and Churg-Strauss syndrome
- Vocal cord dysfunction
- COPD

Therapeutic agents used in asthma

**β2-adrenergic agonists**

- Short-acting (SABA): salbutamol, albuterol. Rapid onset of action and last for up to 6 h. SABAs are effective rescue medications but excessive use indicates inadequate asthma control. SABAs can prevent exercise-induced asthma if administered before exercise.
- Long-acting (LABA): salmeterol and formoterol, have a slower onset of action but last for >12 h.
- Common side effects of β2-adrenergic agonists include muscle tremor and palpitations, arrhythmias
Anticholinergics: ipratropium bromide
Theophylline
Step-wise approach to asthma therapy according to the severity of asthma and ability to control symptoms

Controller therapies
**Inhaled corticosteroids (ICS):** fluticasone, triamcinolone, budesonide, flunisolide, beclomethasone
**Systemic corticosteroids:** prednisolon, methylprednisolon POS or IV should be avoided if at all possible in the chronic management of asthma due to multiple potential side effects.
**Antileukotrienenes:** montelukast, zafirlukast
**Cromolyn sodium, nedocromil sodium:** brief durations of action and typically modest effects.
**Anti-IgE antibody (omalizumab):** given SC.

Hyposensibilisation

Acute exacerbations - Acute severe asthma – Status asthmaticus

**Definition**
Periods of acute worsening of asthma symptoms that may be life-threatening.

**Etiology**
Viral upper respiratory tract infections

**Symptoms**
- Increased dyspnea, wheezing, pulsus paradoxus, tachypnea, tachycardia, and lung hyperinflation.
- Pulmonary function testing
- Reduction in FEV1 and PEF, hypoxemia can result. PCO2 is usually reduced due to hyperventilation.
- Normal or rising PCO2 can signal impending respiratory failure.

**Treatment**
- High doses of SABA (by nebulizer or metered-dose inhaler with a spacer)
- IV or POS corticosteroids, such as methylprednisolone (e.g., 80 mg IV q8h)
- Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%).
- If respiratory failure occurs, mechanical ventilation
- Antibiotics only if bacterial infection is present (rarely)

OCCUPATIONAL ASTHMA

**Definition**
Asthma that occurs in a previously healthy individual as a result of occupational exposure.
Common causes of occupational asthma
Isocyanates, anhydrides (phthalic, trimellitic, tetrachlorophthalic), soldering fluxes, metal salts (Pt, Cr, Ni) wood dusts (red cedar, redwood, zebrawood), plant dusts (grain, coffee bean, castor bean), laboratory animals, shellfish (crab, prawn, oyster), biologic enzymes

Drug allergies
Antibiotics: All, esp. penicillin, amoxicillin, sulphonamides,
Radiographic contrast media: Mostly pharmacological actions caused by hyperosmolarity → activation of complement, release of histamine
Local anesthetics: Toxic, psychophysiologic reactions, contact dermatitis
Aspirin and other NSAID-s: Asthma, rhinorrhea, urticaria
ACE inhibitors: Prolong the effect of bradykinin. Cough, severity of asthma, angioedema ↑
Beta-lactam antibiotic allergy: Amoxicillin rash

THE IMMUNE DEFICIENCIES

Classification of the immune deficiencies
1. Primary immune deficiencies
   a) Primary specific immune deficiencies
      - B cell defects
      - T cell defects
      - Combined defects
      - Severe combined defects
   b) Primary aspecific immune deficiencies
      - Complement defects
      - Phagocyte defects
2. Secondary (acquired) immune deficiencies
3. Transient immune deficiencies

Clinical characteristics of antibody deficiency disorders
- Recurrent infections with high-grade extracellular encapsulated pathogens
- Few problems with fungal or viral (except enterovirus) infections
- Chronic sinopulmonary disease
- Growth retardation not striking
- Antibody deficiency in serum and secretions
- Compatible with survival to adulthood except for those with persistent enterovirus infections, autoimmune disorders or malignancy

Clinical characteristics of cellular immune deficiency disorders
- Recurrent infections with low-grade or opportunistic infectious pathogens such as fungi, viruses, or Pneumocystis carinii
- Delayed cutaneous anergy
- Accompanied with growth retardation, short life span, wasting, and diarrhea
- Susceptible to graft-versus-host (GVH) disease if given fresh blood, plasma, or unmatched allogeneic bone marrow
- Fatal reactions from live virus or BCG vaccination
- High incidence of malignancy
Opportunistic infections in T cell deficiency

Patient selection and identification

- Early diagnosis is vital. Whom to investigate?
- Infants from families known to have hereditary immune deficiency. Infant loss in family.
- Infants whose siblings with possible or established immune deficiency.
- Infants with syndromes or other diseases known to be associated with immune deficiency.
- Infants, who fail to thrive, have unusually persistent infections with low virulence or opportunistic agents, unusual rash, or persistent diarrhea.
- Persistent or recurrent infections that fail to respond as expected to antibiotic therapy:
  Recurrent sinopulmonary infections are commonly the presenting problem.
  Recurrent skin infections, abscesses, periodontitis, or unusual wound healing.
  Recurrent neisserial infections or with SLE.

Family members should also be investigated.

Laboratory assessment of the immune response. 1. Initial screening assays*

A. Complete blood count (incl. qualitative)
   - Granulocyte, lymphocyte, platelet count
   - Howell-Jolly bodies
   - Lymphopenia (< 1500/l is always suspicious in young infants).
   - Wiskott-Aldrich syndrome: thrombopenia, small platelets in male infants
   - Anemia: Coombs positive hemolysis

B. Serum immunoglobulin concentration IgG, IgA, IgM, IgD, IgE
* Together with a history and physical examination, these tests will identify more than 95% of patients with primary immune deficiencies.

Selective IgA deficiency

IgA < 50 mg/dl (both IgA1 and IgA2 are absent); IgG, IgM are normal
Can associate with IgG2 deficiency, autoimmune disorders (RA, SLE), and asthma, atopy: 20-40x
Frequency: 1:600-1:700 in Europe, 1:18500 in Japan
Often familial, more commonly sporadic
Congenital: after intrauterine infections (toxoplasmosis, CMV), or phenytoin or penicillamine
High risk: HLA-A1, B8, DW3. Predisposing gene is on MHC III locus.
Symptoms: From none to severe bronchopulmonary infections, bronchiectasis
Anti-IgA antibodies: risk of anaphylaxis. Transfusion only with blood from IgA-deficient donors!
Ig supplementation is indicated only when IgG deficiency is also present!

The treatment of primary immune deficiencies

1. Bone marrow transplantation (BMT)
   - Combined, severe combined, defect, granulocyte function defect
     - Identical, haplo-identical BMT
     - Stem cell transplantation: Source: bone marrow, peripheral blood, umbilical cord blood
     - Intrauterine transplantation of parental stem cells: in XL-SCID

2. Immunoglobulin replacement
   - I.V. Ig is life saving! Pooled Ig or IgG preparates. Dose: 400-500 mg/kg monthly.
Untoward reactions: Anaphylactic reaction due to Ig aggregates, excessively fast flow rate of infusion, rarely to anti-IgA antibodies. HIV, lipid-coat viruses are effectively excluded but HCV has been reported.

3. Enzyme replacement
Bovine ADA + PEG I.M. weekly. Gene therapy: ADA gene cloned in a retroviral vector

4. Treatment of opportunistic infections
- Early, full-dose antibiosis is needed.
- Narrow-spectrum drugs selected on microbial sensitivity testing should be used.
- Short-term prophylactic antibiotics increase the hazard of infections with fungi or other resistant organisms. Long-term treatment with combination sulfa drugs and itraconazole may be of some benefit.

Vaccination in primary immune deficiencies
- Living vaccine (e.g. BCG, poliomyelitis, measles, rubella, mumps) should not be given when primary immune deficiency is even suspected not even to family members!
- Living vectors are also contraindicated!
- Antituberculotic treatment should be started following BCG vaccination of infants with primary cellular immune deficiency!

Causes of secondary immune deficiencies
- Malnutrition
- Deficiency of vitamins (A and C) and trace elements (Se, Zn)
- Infectious diseases:
  - chronic bacterial: (e.g. TBC, leprosy)
  - following viral infections (e.g. varicella, measles, rubella)
  - fungal (e.g. Candida)
  - parasitic (e.g. malaria)
- Excessive protein loss (with loss of g-globulins):
  - nephrotic syndrome
  - protein-losing enteropathy, intestinal lymphangiectasia
- Toxic effects:
  - Immunosuppression (irradiation, drugs, anti-lymphocyte serum)
  - following major surgery
  - intoxications (environmental agents)
- Uremia
- Malignant lymphomas
- Metastatic solid tumors
- Pregnancy
- Old age
- Diabetes mellitus
- HIV infection